OPPT-2003-0016-0024

CLA Supports 2-Generation Rat Reproduction as a Tier 2 Test

- **As a definitive test following Tier 1 screening**
- **As a Tier 1 by-pass option – by choice and for pesticides**
- **No short cuts on validation**

CLA Supports Validation 2-Gen Rat Reproduction as Tier2 Test

- **Critical that this test is sufficiently sensitive and robust to either confirm or determine/eliminate concerns for adverse endocrine effects**
  - Differentiate endocrine effects from dose related systemic toxicity.
- **CLA urges EPA/EDMVS to consider relevance/value of all additional endpoints**
- **Differentiate endpoints that should be conducted routinely vs. those that should be triggered**
  - E.G. thyroid hormones & histopathology
  - Extensive F1 adult male necropsy unless triggered by anti-androgenic observations in weanlings
- **Critical that the revised test is demonstrated and validated in its entirety**

Rat 2-Gen Reproduction Test Is Already Complex and Resource Intensive

- **Typically, the test uses 3,040 rats, 18 months (in-life and follow-on pathology only) and costs >> $500K**
  - Typically conducted after 90 Day previously to inform doses and target tissues
- **Support case-by case evaluation of whether it is necessary to repeat older studies or address gaps**
- **Other alternatives:**
  - 1-gen study to bridge 2-gen data gaps
  - Thyroid endpoints in short-term/subchronic tests, pubertal/14 day intact male assays or short-term 28 day repeated dose studies

CLA Concerns

- **At present, insufficient evidence to support extension/ additional animals in the 2-gen repro study solely for ED effects**
  - In utero exposure issue being evaluated in other forums
  - Coordinate with other EPA/ government programs
  - Consider international harmonization issues
- **Clarify use and value of one-generation rat in utero lactation assay**
  - Useful or confounding data?
  - Redundant with other tests?
  - How will these data be used to determine ED and or in risk assessment?
  - Is not a half of a 2-gen, assay still needs to be demonstrated and validated

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